11.(amended) The kit according to claim 10, wherein the reagent for isolating the LDL from the serum or plasma sample is a buffered heparin solution.

12.(amended) The kit according to claim 10, wherein the reagent for separating the lipid is a chloroform-methanol solution.

13.(amended) The kit according to claim 10, wherein the reagent for use in the determination of LDL-BDC in the lipid fraction is an organic solvent.

14.(amended) The kit according to claim 13, wherein the reagent for use in the determination of LDL-BDC in the lipid fraction is a cyclohexane.

15.(amended) The kit according to claim 10, wherein the reagent for use in the determination of the antioxidant potential of LDL is the sample is 2,2' -azobis(2-amidinopropane)HCl (ABAP).

Remarks

Applicant has amended the Abstract to present it in a single paragraph and to remove the "legal phraseology," which Applicant assumes to be the terms "comprises" and "comprising". These terms have been replaced with the terms "includes" and "including."

Applicant has provided herewith for the Examiner a copy of the Declaration as filed with the application.

The claims have been amended to remove the term "means" found objectionable by the Examiner. The term "reagent" has been substituted in its place in the claims. The typographical error in claim 3 has been fixed.

Rejections Under 35 USC 103(a)

1. Claims 1-6, 16-19 and 25

The Examiner has rejected claims 1-6, 16-19 and 25 under 35 USC 103(a) as unpatentable over the combination of Wieland and Vasankari. Applicants respectfully traverse the rejection.

The references cited by the Examiner do not teach or suggest the elements of the invention claimed in claims 1-6, 16-19 and 25. First, the Wieland reference describes the selective precipitation of low density lipoproteins (LDL) from other plasma proteins (see abstract and first full paragraph, right column, p. 904), not an LDL lipid fraction as is presently claimed. On page 908 Wieland states that "the determination of plasma LDL by precipitation" is a technique suitable for mass screening due to "the pathophysiological importance of LDL in atherogenesis," (see paragraph spanning left and right columns) Thus Weiland is not concerned with the analysis of the LDL lipid fraction.

Second, the Vasankari reference describes separation of lipids of whole serum, again not an LDL lipid fraction as is presently claimed in claims 1-6, 16-19 and 25. The Vasankari reference teaches only that lipids are extracted from raw blood serum with organic solvent and then analyzed spectrophotometrically. The claimed invention calls for isolating the LDL from a serum or plasma and then separating the subject lipids. The Vasankari reference teaches that any and all lipids, both LDL and non-LDL, should be extracted indiscriminately from a blood sample and then analyzed by some spectrographic method which does not provide an analysis of LDL oxidizability.

The Vasankari reference teaches away from the present invention. Blood contains numerous lipids and lipoproteins. Analyzing a raw blood sample does not provide an accurate, if any, measure of LDL oxidizability, but rather only provides a generic analysis which is based on the presence of all lipids, lipoproteins and all other molecules which are indiscriminately extracted from the blood sample. The invention as claimed is clearly not obvious in view of the Vasankari reference.

Vasankari or other references, but which the Vasankari reference suggests are irrelevant or unnecessary. It is submitted that it would require extraordinary modification and/or invention over the disclosure of the Vasankari reference render the present invention obvious.

The Examiner stated that selection of "the method of Vasankari would have been obvious because it would have the expected result." Office Action at page 4. Applicants respectfully disagree, for the reasons presented above. In particular, Vasankari teaches only that lipids are extracted from raw blood serum with organic solvent and then analyzed spectrophotometrically. The claimed invention, in contrast, requires the isolation of the LDL from a serum or plasma and then separation of lipids. Thus one of ordinary skill in the art would not have looked to Vasankari, because Vasankari was concerned with isolation of lipids from a completely different source.

Therefore, the combination of the Weiland reference and the Vasankari reference do not provide the elements of the claimed invention. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1-6, 16-19 and 25 under 35 USC 103(a).

2. Claims 7-15 and 20-24

The Examiner has rejected claims 7-15 and 20-24 under 35 USC 103(a) as unpatentable over the combination of Wieland and Vasankari, further in view of Seccia and Valkonen for their teaching of the use of ABAP. Applicants respectfully traverse the rejection.

First, the shortcomings of the combination of the Wieland and Vasankari references are described above.

Second, neither the Seccia reference nor the Valkonen reference provide the elements missing from the combination of the Wieland and Vasankari references. In particular, the Valkonen reference describes the measurement of TRAP in serum samples, not in a LDL fraction as is claimed. Seccia achieved separation of LDL from serum using gradient ultracentrifugation. Thus these references do not provide the missing elements of the claimed invention, and further would not likely be combined with the Wieland and Vasankari references in any case, due to the differences in the teachings of these several references.

Further differences between the presently claimed invention and the prior art include the

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detection and that of Valkonen is based on spectrophotometric and fluorometric detection systems. The use of chemiluminescence has several advantages over the prior art procedures. (1) The assay procedure is considerably faster: in the claimed system the lag time is about 10 minutes for a normal LDL sample; the lag time in Seccia is about 57 minutes and the lag time for Valkonen is over 40 minutes. (2) Due to the higher sensitivity, less sample is required. (3) Due to the higher sensitivity, determination of the lag time is much more accurate in the presently claimed system (see specification, page 2) than with the other methods (Valkonen, Figs. 1-3 and 5).

Third, in addition to the lack of the elements of the claimed invention in the cited prior art, the Examiner has not provided a valid reason for making the combination of Seccia and/or Valkonen with the Wieland and Vasankari references. The Examiner stated on page 5 of the Office Action that it would have been obvious to use the methods of Seccia and/or Valkonen with the Wieland and Vasankari references "because determining the antioxidant potential of separated dienes with ABAP is taught by each of Seccia and Valkonen." The mere description of a particular method by a reference does not provide a motivation to combined the reference with another reference in a combination for an obviousness rejection. The Examiner must provide a basis for making the combination that is recognized in the law.

It is not clear at all from the Office Action why one of ordinary skill in the art would have been motivated to combine the teachings of the cited prior art to reach the claimed invention. The Examiner has not provided an explanation of the motivation to combine the teachings that one of ordinary skill in the art would have had.

The requirement for a specific motivation to combine the teachings of prior art references was most recently set forth by the Court of Appeals for the Federal Circuit in In re Sang Su Lee. Applicants provide below an excerpt for the convenience of the Examiner.

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. See, e.g., McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).
>
> "The factual inquiry whether to combine references must be thorough and

1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting C.R. Bard, Inc., v. M3 Systems, Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined only if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

The need for specificity pervades this authority. See, e.g., In re Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references").

In re Sang Su Lee, slip op. 7-9 (Fed. Cir. 2002) (emphasis added except where noted)

Therefore the obviousness rejection also fails because the Examiner has not provided motivation to combine based on objective evidence of record.

Rejections Under 35 USC 112, Second Paragraph

The Examiner has rejected claims 1-25 under 35 USC 112, second paragraph, as indefinite.

The rejections relating to the use of "means" in kit claims and the typographical error have been obviated by amendments to the claims.

The rejection of claim 25 relating to instructions provided with the kit is traversed. The Examiner stated that the instructions limitation is improper, but not why this [illegible]

Based on the foregoing claim amendments and arguments, Applicants respectfully request that the Examiner withdraw the rejections of claims 1-25 under 35 U.S.C. §112, second paragraph.

Applicants believe the application is now in condition for allowance. If the Examiner does not find the foregoing amendments and arguments to place the claims in conditions for allowance, then the Examiner is respectfully invited to contact Applicants' representative at the number listed below.

Respectfully submitted,

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Attorney's Docket No.: O00013/70075
Date: April 18, 2002
X04/18/02

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Marked-up Paragraphs of Specification

Kits are provided for use in the screening of the risk for, the diagnosis, management and research of atherosclerosis and coronary heart disease comprising means for isolating LDL from a serum or plasma sample for the preparation of a LDL fraction, and means for separating the lipids from the LDL fraction to obtain a lipid fraction. The kit can further [comprise] include a means for use in the determination of the baseline level of conjugated dienes (LDL-BDC) in the lipid fraction.[

]The invention also relates to a kit for use in the above mentioned purpose [comprising] including means for isolating LDL from a serum or plasma sample for the preparation of a LDL fraction, and means for use in the determination of the antioxidant potential of LDL in the sample.[

]The invention further provides a kit for use in the above mentioned purpose [comprising] including means for isolating LDL from a serum or plasma sample for the preparation of a LDL fraction, means for separating the lipids from the LDL fraction to obtain a lipid fraction, means for use in the determination of LDL-BDC in the lipid fraction, and means for use in the determination of the antioxidant potential of LDL in the sample.[

]Additional kits and improved methods for analysis of LDL-BDC and/or LDL-TRAP are provided.

Marked-up Claims

1.(amended) A kit for use in the screening of the risk for, the diagnosis, management and research of atherosclerosis and coronary heart disease comprising

[-means] a container containing a reagent for isolating LDL from a serum or plasma sample for the preparation of a LDL fraction, and

[-means] a container containing a reagent for separating the lipids from the LDL fraction to obtain a LDL lipid fraction.

3.(amended) The [it] kit according to claim 1, wherein the [means] reagent for separating the lipid is a chloroform-methanol solution.

4.(amended) The kit according to claim 1, further comprising a [means] reagent for use in the determination of the baseline level of conjugated dienes (LDL-BDC) in the lipid fraction.

5.(amended) The kit according to claim 4, wherein the [means] reagent for use in the determination of LDL-BDC in the lipid fraction is an organic solvent.

6.(amended) The kit according to claim 4, wherein the [means] reagent for use in the determination of LDL-BDC in the lipid fraction is cyclohexane.

7.(amended) A kit for use in the screening of the risk for, the diagnosis, management and research of atherosclerosis and coronary heart disease comprising

[means] a container containing a reagent for isolating LDL from a serum or plasma sample for the preparation of a LDL fraction, and

[means] a container containing a reagent for use in the determination of the antioxidant potential of LDL (LDL-TRAP) in the LDL fraction.

8.(amended) The kit according to claim 7, wherein the [means] reagent for isolating the LDL from the sample is a buffered heparin solution.

9.(amended) The kit according to claim 7, wherein the [means] reagent for use in the determination of the antioxidant potential of LDL in a serum or plasma sample is 2,2' -azobis(2-amidinopropane)HCl (ABAP).

10.(amended) A kit for use in the screening of the risk for, the diagnosis, management and research of atherosclerosis and coronary heart disease comprising

[means] a container containing a reagent for separating the lipids from the LDL fraction to obtain a lipid fraction,

[means] a container containing a reagent for use in the determination of LDL-BDC in the lipid fraction, and

[means] a container containing a reagent for use in the determination of LDL-TRAP in the LDL fraction.

11.(amended) The kit according to claim 10, wherein the [means] reagent for isolating the LDL from the serum or plasma sample is a buffered heparin solution.

12.(amended) The kit according to claim 10, wherein the [means] reagent for separating the lipid is a chloroform-methanol solution.

13.(amended) The kit according to claim 10, wherein the [means] reagent for use in the determination of LDL-BDC in the lipid fraction is an organic solvent.

14.(amended) The kit according to claim 13, wherein the [means] reagent for use in the determination of LDL-BDC in the lipid fraction is a cyclohexane.

15.(amended) The kit according to claim 10, wherein the [means] reagent for use in the determination of the antioxidant potential of LDL is the sample is 2,2' -azobis(2-amidinopropane)HCl (ABAP).